

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**20-372/S-013**

**Approved Labeling**

**MYOVIEW™**  
**(Kit for the Preparation of Technetium-99m Tetrofosmin for Injection)**

**NDA 20-372**  
**SUPPLEMENTAL NDA**

**ITEM 2**  
**DRAFT LABELING**

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**Confidentiality Statement**

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**MYOVIEW™** Code N166A  
**Kit for the Preparation of Technetium Tc99m**

## **Tetrofosmin for Injection**

### **Diagnostic Radiopharmaceutical**

**For intravenous use only**

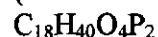
**Rx ONLY**

### **DESCRIPTION**

The MYOVUE kit is supplied as a pack of five vials for use in the preparation of a technetium Tc99m tetrofosmin intravenous injection to be used for the scintigraphic delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium and for evaluation of ventricular function. Each vial contains a predispensed, sterile, non-pyrogenic, lyophilized mixture of 0.23 mg tetrofosmin (6,9-bis [2-ethoxyethyl]-3,12-dioxo-6, 9-diphosphatetradecane), 30 µg stannous chloride dihydrate (minimum stannous tin 5.0 µg; maximum total stannous and stannic tin 15.8 µg), 0.32 mg disodium sulphosalicylate and 1.0 mg sodium D-gluconate, and 1.8 mg sodium hydrogen carbonate. The lyophilized powder is sealed under a nitrogen atmosphere with a rubber closure. The product contains no antimicrobial preservative.

The structural formula of tetrofosmin is:

### **(CHEMICAL STRUCTURE)**



When sterile, pyrogen-free sodium pertechnetate Tc99m in isotonic saline is added to the vial, a Tc99m complex of tetrofosmin is formed.

Administration is by intravenous injection for diagnostic use.

### **Physical Characteristics**

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.03 hours<sup>(1)</sup>. Photons that are useful for imaging studies are listed in Table 1.

**Table 1**

**Principal radiation emission data - technetium Tc99m**

<b>Radiation</b>	<b>Mean % /disintegration</b>	<b>Mean energy (keV)</b>
Gamma 2	87.87	140.5

- 1) Dillman, L.T. and Von der Lage, F.C. Radionuclide decay schemes and nuclear parameters for use in radiation-dose estimation. MIRD Pamphlet No. 10, P62, 1975.

### **External Radiation**

The specific gamma ray constant for technetium Tc99m is 206 microCoulomb.kg<sup>-1</sup>/37 MBq-hr (0.8 R/mCi-hr) at 1 cm. The first half-value thickness of lead (Pb) for technetium Tc99m is 0.2mm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of Pb is shown in Table 2. For example, the use of a 2.7mm thickness of Pb will decrease the external radiation exposure by a factor of 1000.

**Table 2****Radiation attenuation by lead shielding**

Shield thickness (Pb) mm.	Coefficient of attenuation
0.2	0.5
0.95	$10^{-1}$
1.8	$10^{-2}$
2.7	$10^{-3}$
3.6	$10^{-4}$
4.5	$10^{-5}$

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals relative to the time of calibration are shown in Table 3.

**Table 3****Physical decay chart - Tc99m half-life 6.03 hours**

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.399
2	0.795	9	0.355
3	0.708	10	0.317
4	0.631	11	0.282
5	0.563	12	0.252
6	0.502	24	0.063

\*Calibration time (time of preparation)

**CLINICAL PHARMACOLOGY****General**

When technetium Tc99m pertechnetate is added to tetrofosmin in the presence of stannous reductant, a lipophilic, cationic technetium Tc99m complex is formed, Tc99m tetrofosmin. This complex is the active ingredient in the reconstituted drug product, on whose biodistribution and pharmacokinetic properties the indications for use depend.

**Pharmacokinetics**

Studies in normal volunteers have demonstrated rapid myocardial uptake of Tc99m tetrofosmin, and rapid blood, liver and lung clearances. Uptake in the myocardium reaches a maximum of about 1.2% of the injected dose (i.d.) at 5 minutes and approximately 1% of the i.d. at 2 hours, respectively. Background activities in the blood, liver, and lung were less than 5% of the administered activity in whole blood at

10 minutes post-injection, less than 4.5% i.d., after 60 minutes, and less than 2% i.d. after 30 minutes. Approximately 66% of the injected activity is excreted within 48 hours post-injection, with approximately 40% excreted in the urine and 26% in the feces.

The kinetics, elimination, and protein binding of Tc99m tetrofosmin have not been determined.

**Pharmacodynamics**

The pharmacodynamic cellular uptake of tetrofosmin in humans has not been established. In humans the recommended imaging time is 15 minutes at stress and 30 minutes at rest.

## Metabolism

The metabolic profile of tetrofosmin has not been established.

## Drug-Drug Interactions

Specific drug-drug interactions have not been studied.

## Clinical Studies

### 1. Exercise Stress Studies

A total of 252 subjects with ischemic heart disease or atypical chest pain who had a reason for exercise stress imaging were studied in two open-label, multi-center, clinical studies of Tc99m tetrofosmin (study a and study b). Of these 252 subjects there were 212 (84%) male and 40 (16%) female, with a mean age of 60.5 years (range 33.7 to 82.4 years). At peak exercise, maximum heart rate achieved and peak systolic blood pressure were comparable after MYOVUE and thallium-201 exercise studies.

All subjects had exercise and rest planar imaging with MYOVUE and thallium-201; 191 (76%) subjects also had single photon emission computed tomography (SPECT) imaging. The MYOVUE and thallium-201 images were separated by a mean of 5.1 days (1-14 days before or 2-14 days after MYOVUE). For MYOVUE imaging, each subject received 185-296 MBq (5-8 mCi) Tc99m tetrofosmin at peak exercise and 555-888 MBq (15-24 mCi) Tc99m tetrofosmin at rest approximately 4 hours later. For thallium-201 imaging, subjects received thallium-201 55.5-74 MBq (1.5-2.0 mCi) at peak exercise.

The images were evaluated for the quality of the image (excellent, good or poor) and the diagnosis (with scores of 0 = normal, 1 = ischemia, 2 = infarct, 3 = mixed infarct and ischemia). The primary outcome variable was the percentage of correct diagnoses in comparison to the final clinical diagnosis.

All planar images were blindly read; SPECT images were evaluated by the unblinded investigator. A subset of 181/252 (72%) subjects had coronary angiography comparisons to the planar images of MYOVUE or thallium-201.

In comparison to the clinical diagnosis, results of MYOVUE and thallium-201 imaging were comparable within the 95% confidence intervals. The results for each blinded reader are noted in the following table.

### OVERALL DIAGNOSTIC OUTCOME

Total percentage thallium-201 MYOVUE™ correctly diagnosed

	Readers 1, 2	Readers 1, 2
Ischemia		
Study a	77.7%,75.0%	66.3%,63.6%
Study b	75.6%,68.9%	66.4%,66.4%
Infarct		
Study a	75.9%,75.0%	75.9%,75.0%
Study b	70.6%,69.7%	73.1%,68.1%

### 2. Pharmacologic Stress Studies

MYOVUE imaging after pharmacologic stress was evaluated in two studies in subjects with known or suspected coronary artery disease (CAD). Three blinded reads were obtained for 57 subjects (45 male [79%], 12 female [21%]); mean age 60.1 years) all of whom had angiography. A subset of 19 subjects

also had Thallium-201 SPECT imaging. Subject level analyses were based on the finding of SPECT myocardial perfusion abnormalities in subjects with angiographically confirmed disease. Subject level sensitivities for MYOVUE ranged from 68 to 83% across readers and studies. Subject level sensitivities for Thallium-201 ranged from 79-89% across readers.

### **3. Ventricular Function Studies**

Two open-label, multicenter, identically designed, blinded image read clinical studies were conducted to assess left ventricular function using MYOVUE ECG gated SPECT (GSPECT) myocardial perfusion imaging. A total of 329 subjects (216 male [65.7%], 113 female [34.3%]); mean age of 60.4 years) with known or suspected heart disease or requiring ventricular function assessments were dosed with MYOVUE. Of these 297 were considered evaluable. Myovue was administered at rest and at peak stress using either a one-day or a 2-day dosing protocol.

For both studies, all subjects' stress GSPECT exams were compared to the reference exam of radionuclide ventriculography with Tc-99m labeled RBCs (multiple gated acquisition [MUGA]), performed 1 to 5 days after the second MYOVUE injection. All subjects' GSPECT exams were assessed by 3 independent blinded readers per study. The MUGA exams were evaluated as a truth standard by an independent consensus panel composed of 3 blinded readers. Subject level assessments were based upon discrimination between normal and abnormal values for LVEF (LVEF  $\geq 50\%$  was considered normal) and normal and abnormal wall motion as judged visually. Sensitivity and specificity of LVEF determinations ranged from 81%-88% and 76% to 85% respectively (across studies and readers). Sensitivity and specificity of wall motion determinations ranged from 80%-92% and 68%-86% respectively (across studies and readers). In an analysis of LVEF by severity of dysfunction (i.e. mild dysfunction 40%-49%, moderate dysfunction 30%-39%, severe dysfunction of  $<30\%$ ), across subgroups there was individual reader variation in agreement with MUGA. These studies were not designed to determine whether differences between GSPECT and MUGA LVEF values were due to over estimation or under estimation by either of the methods.

### **INDICATIONS AND USAGE**

MYOVUE is indicated for scintigraphic imaging of the myocardium following separate administrations under exercise and /or resting conditions. It is useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium.

MYOVUE is also indicated for scintigraphic imaging of the myocardium to identify changes in perfusion induced by pharmacologic stress in subjects with known or suspected coronary artery disease.

MYOVUE is also indicated for the assessment of left ventricular function (left ventricular ejection fraction and wall motion) in subjects being evaluated for heart disease.

### **CONTRAINDICATIONS**

None known.

### **WARNINGS**

In studying subjects with known or suspected coronary artery disease, care should be taken to ensure continuous cardiac monitoring and the availability of emergency cardiac treatment.

Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Caution should be used when pharmacologic stress is selected as an alternative to exercise; it should be used when indicated and in accordance with the pharmacologic stress agent's labeling.

## **PRECAUTIONS**

### **General**

To minimize radiation dose to the bladder, the subject should be encouraged to void when the examination is completed and as often thereafter as possible. Adequate hydration should be encouraged to permit frequent voiding.

The contents of the MYOVUE vial are intended only for use in the preparation of MYOVUE injection and are NOT to be administered directly to the subject.

As with all injectable drug products, allergic reactions and anaphylaxis may occur.

Sometimes Tc99m labeled myocardial imaging agents may produce planar and SPECT images with different imaging information.

In patients who have a Myovue GSPECT LVEF value or wall motion assessment that is not consistent with the clinical status, additional evaluations with other modalities should be considered as appropriate.

MYOVUE injection, like other radioactive drugs, must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to the subject consistent with proper subject management.

Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

**Drug Interactions:** Drug interactions were not noted and were not studied in clinical studies in which MYOVUE was administered to subjects receiving concomitant medication. Drugs such as beta blockers, calcium blockers and nitrates may influence myocardial function and blood flow. The effects of such drugs on imaging results are not known.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Studies have not been conducted to evaluate carcinogenic potential or effects on fertility.

Tetrofosmin sulphosalicylate was not mutagenic *in vitro* in the Ames test, mouse lymphoma, or human lymphocyte tests, nor was it clastogenic *in vivo* in the mouse micronucleus test.

### **Pregnancy Category C**

Animal reproduction studies have not been conducted with MYOVUE. It is not known whether

MYOVUE can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Therefore, MYOVUE should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.

### **Nursing Mothers**

Technetium Tc99m pertechnetate can be excreted in human milk. Therefore, formula should be substituted for breast milk until the technetium has cleared from the body of the nursing woman.

### **Pediatric Use**

Safety and effectiveness in pediatric subjects have not been established.

### **ADVERSE REACTIONS**

Adverse events were evaluated in clinical studies (using an exercise/rest protocol) of 764 adults (511 men and 253 women, with a mean age of 58.7 years (range 29-94 years). The subjects received a mean dose of 7.67 mCi on the first injection and 22.4 mCi on the second injection of MYOVUE.

Deaths did not occur during the clinical study period of 2 days. Six cardiac deaths occurred 3 days to 6 months after injection and were thought to be related to the underlying disease or cardiac surgery. After MYOVUE injection, serious episodes of angina occurred in 4 subjects, ventricular tachycardia in one subject, and respiratory arrest in one subject. The respiratory arrest occurred within minutes of MYOVUE and pharmacologic stress dosing in a subject with underlying pulmonary disease. The patient was treated and fully recovered. Whether this event was caused by underlying disease or concurrent use of MYOVUE injection and a pharmacologic stress agent cannot be determined.

Overall, cardiac adverse events occurred in less than 1% of subjects after MYOVUE injection.

The following events were noted in less than 1 % of subjects:

Cardiovascular: angina, hypertension, Torsades de Pointes.

Gastrointestinal: vomiting, abdominal discomfort.

Hypersensitivity: cutaneous allergy, hypotension, dyspnea.

Special Senses: metallic taste, burning of the mouth, smell alteration.

There was a low incidence (less than 4%) of a transient and clinically insignificant rise in white blood cell counts following administration of the agent.

Adverse events were also evaluated in clinical studies using pharmacologic stress. In four studies of 438 adults (232 men and 205 women: gender was not recorded for one subject) with a mean age of 65.4 years (range 27-97 years; age was not recorded for two subjects) received a single pharmacologic stress agent. The subjects received a mean dose of 7.46-7.79 mCi on the rest/first injection and 22.12-33.79 mCi on the stress/second injection.

Among the 438 subjects, 319 experienced an adverse event (73%). Events occurring in  $\geq 1\%$  of the subjects included angina (39%), flushing (36%), dyspnea (28%), headache (14%), abdominal pain (11%), dizziness (7%), palpitations (2%), nausea (2%), hypotension (1%), and pain (1%). Events occurring in  $< 1\%$  include cough, arrhythmia, bronchospasm, ECG abnormalities, hypertension, vomiting and asthenia. Attribution of the above events to MYOVUE and/or the pharmacologic stress agent cannot be determined due to study design.



In additional ventricular function studies with 1 and 2 day dosing protocols, the overall adverse event profile was similar to previous reports and included one patient who was withdrawn for syncope.

**Post marketing experience:** The following are spontaneously reported adverse reactions from post-marketing experience. Because the reports cite reactions reported spontaneously from worldwide post-marketing experience, frequency of reactions and the role of MYOVUE in their causation cannot be reliably determined. The most common adverse reactions reported included the following: rash, urticaria, abnormal vision, allergic reactions, and fever.

## **DOSAGE AND ADMINISTRATION**

The recommended dose range for MYOVUE is 5-33mCi (185-1221 MBq).

For stress and rest imaging, 2 separate doses of MYOVUE are used. When rest and stress injections are administered on the same day, the first dose should be 5-12 mCi (185-444 MBq) and followed by the second dose of 15-33 mCi (555-1221 MBq) given approximately 1 to 4 hours later.

Imaging may begin 15 minutes following administration of the agent.

Dose adjustment has not been established in renally or liver impaired, pediatric or geriatric subjects.

## **RADIATION DOSIMETRY**

Based on human data, the absorbed radiation doses to an average human adult (70 kg) from intravenous injections of the agent under exercise and resting conditions are listed in Table 4. The values are listed in descending order as rad/mCi and  $\mu$ Gy/MBq and assume urinary bladder emptying at 3.5 hours.

**Table 4**

**Estimated Absorbed Radiation Dose (Technetium Tc99m Tetrofosmin Injection)**

Target organ	Absorbed radiation dose			
	Exercise		Rest	
	rad/mCi	$\mu$ Gy/MBq	rad/mCi	$\mu$ Gy/MBq
Gall bladder wall	0.123	33.2	0.180	48.6
Upper large intestine	0.075	20.1	0.113	30.4
Bladder wall	0.058	15.6	0.071	19.3
Lower large intestine	0.057	15.3	0.082	22.2
Small intestine	0.045	12.1	0.063	7.0
Kidney	0.039	10.4	0.046	12.5
Salivary glands	0.030	8.04	0.043	11.6
Ovaries	0.029	7.88	0.035	9.55
Uterus	0.027	7.34	0.031	8.36
Bone surface	0.023	6.23	0.021	5.58
Pancreas	0.019	5.00	0.018	4.98
Stomach	0.017	4.60	0.017	4.63
Thyroid	0.016	4.34	0.022	5.83
Adrenals	0.016	4.32	0.015	4.11
Heart wall	0.015	4.14	0.015	3.93
Red marrow	0.015	4.14	0.015	3.97
Spleen	0.015	4.12	0.014	3.82
Muscle	0.013	3.52	0.012	3.32
Testes	0.013	3.41	0.011	3.05
Liver	0.012	3.22	0.015	4.15

Thymus	0.012	3.11	0.009	2.54
Brain	0.010	2.72	0.008	2.15
Lungs	0.008	2.27	0.008	2.08
Skin	0.008	2.22	0.007	1.91
Breasts	0.008	2.22	0.007	1.83

Dose calculations were performed using the standard MIRD method (MIRD Pamphlet No.1 (rev), Society of Nuclear Medicine, 1976). Effective dose equivalents (EDE) were calculated in accordance with ICRP 53 (Ann. ICRP 18 (1-4), 1988) and gave values of  $8.61 \times 10^{-3}$  mSV/MBq and  $1.12 \times 10^{-2}$  mSV/MBq after exercise and rest, respectively.

## **INSTRUCTIONS FOR THE PREPARATION OF MYOVUE INJECTION USE ASEPTIC TECHNIQUE THROUGHOUT.**

The user should wear waterproof gloves and use shielding at all times when handling the reconstituted vial or syringes containing the radioactive agent.

The subject dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

- 1) Place one of the vials in a suitable shielding container and sanitize the rubber septum with the swab provided. Insert a sterile needle (the venting needle) through the rubber septum.
- 2) Using a shielded, 10 mL sterile syringe, inject the required activity of up to 240 mCi (8.8 GBq) technetium Tc99m generator eluate (diluted with Sodium Chloride Injection, USP) into the shielded vial (see Cautionary notes 1 and 2). Before removing the syringe from the vial, withdraw 2 mL of gas from above the solution. Remove the venting needle. Mix gently for 10 seconds to ensure complete dissolution of the powder.
- 3) Incubate at room temperature for 15 minutes
- 4) Assay the total activity, complete the user radiation label, and attach it to the vial.
- 5) Visually inspect the reconstituted solution at a safe distance through leaded glass. Do not use if it is not clear or if it contains foreign particulate matter.
- 6) Maintain adequate shielding of the radioactive preparation.
- 7) Store the reconstituted injection at 2-25°C (36-77°F), and use within 12 hours of preparation.

### **Cautionary notes:**

- 1) The volume of (diluted) technetium Tc99m generator eluate added to the vial must be in the range 4-8 mL.
- 2) The radioactive concentration of the (diluted) Tc99m generator eluate must not exceed 30 mCi/mL (1.1 GBq/mL) when it is added to the vial.
- 3) The pH of the prepared injection should be in the range 7.5-9.0.
- 4) Safety and effectiveness of MYOVUE Injection were established using investigational material shown to have a radiochemical purity of at least 90% prior to administration to subjects in clinical studies.
- 5) The contents of the MYOVUE vial are not radioactive. However, after the sodium pertechnetate Tc99m is added adequate shielding of the final preparation must be maintained.
- 6) The technetium Tc99m labeling reaction involved in the preparation of MYOVUE injection depends on maintaining tin in the divalent (reduced) state. Any oxidant present in the sodium pertechnetate Tc99m used may adversely affect the quality of the preparation. Sodium pertechnetate Tc99m containing oxidants should not be used for the preparation of the labeled

product.

- 7) Sodium Chloride Injection, USP, must be used as the diluent. Do not use bacteriostatic sodium chloride as a diluent for sodium pertechnetate Tc99m injection because it may adversely affect the radiochemical purity and hence the biological distribution of the MYOVUE injection.
- 8) The contents of the MYOVUE vial are sterile and pyrogen-free. The vial contains no bacteriostatic preservative. It is essential that the user follows the directions carefully and adheres to aseptic procedures during the preparation of the radiopharmaceutical.

### Quality Control

An assay of the radiochemical purity of the prepared injection can be performed using the following chromatographic procedure.

### Equipment and eluent

- 1) Gelman ITLC/SG strip (2 cm x 20 cm)
- 2) Ascending chromatography tank and cover
- 3) 35:65 v/v mixture of acetone and dichloromethane
- 4) 1 mL syringe with 22-25 G needle
- 5) Suitable counting equipment

### Method

- 1) Pour the 35:65 acetone: dichloromethane mixture into the chromatography tank to a depth of 1 cm. Cover the tank and allow to equilibrate with the solvent vapor.
- 2) Mark an ITLC/SG strip with a pencil line at 3 cm from the bottom and, using an ink marker pen, at 15 cm from the pencil line. The pencil line indicates the origin where the sample is to be applied and movement of color from the ink line will indicate the position of the solvent front when upward elution should be stopped.
- 3) Cutting positions at 3 cm and 12 cm above the origin (R<sub>f</sub>s 0.2 and 0.8 respectively) should also be marked in pencil.
- 4) Using a 1 mL syringe and needle, apply a 10-20 µL sample of the prepared injection at the origin of the ITLC/SG. Place it in the chromatography tank immediately and replace the cover. Ensure that the strip is not adhering to the walls of the tank.

**Note:** A 10-20 µL sample will produce a spot with a diameter of 7-10 mm.

Smaller sample volumes have been shown to give unreliable radiochemical purity values.

- 5) When the solvent reaches the ink line, remove the strip from the tank, and allow it to dry.
- 6) Cut the strip into 3 pieces at the marked cutting positions and measure the activity on each using suitable counting equipment. Try to ensure similar counting geometry for each piece and minimize equipment dead time losses.
- 7) Calculate the radiochemical purity from:

$$\begin{aligned} \% \text{ MYOVUE} = \\ \frac{\text{Activity of center piece}}{\text{Total activity of all 3 pieces}} \times 100 \end{aligned}$$

A value of at least 90% should be obtained in a satisfactory preparation.

**Note:** Free Tc99m pertechnetate runs to the top piece of the strip. MYOVUE runs to the center piece of the strip. Reduced hydrolyzed Tc99m and any hydrophilic complex impurities remain at the origin in

the bottom piece of the strip.

#### **HOW SUPPLIED**

The kit comprises **five vials** containing a sterile, non-pyrogenic, freeze dried mixture of tetrofosmin, stannous chloride dihydrate, disodium sulphosalicylate, sodium D-Gluconate and sodium hydrogen carbonate, together with appropriate number of radiation labels, sanitizing alcohol swabs and a package insert.

#### **STORAGE**

Store the kit in a refrigerator at 2-8°C (36-46°F). Store the reconstituted product at 2-25°C (36-77°F), using appropriate radiation shielding. The kit should be protected from light.

This reagent kit is approved for use by persons licensed by the Illinois Department of Nuclear Safety pursuant to 32 Ill. Code Adm. Section, Section 330.260(a) and 335.4010 or under equivalent licenses of the U.S. Nuclear Regulatory Commission, or an Agreement State.

#### **Manufactured by:**

Amersham plc  
Amersham, United Kingdom  
Patent No. 5,045,302 (r)

#### **Distributed by:**

Medi-Physics, Inc.,  
Arlington Heights, IL 60004  
1-800-633-4123 (Toll Free)  
Printed in UK

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May 2002

43-1011C

82 pages redacted from this section of  
the approval package consisted of draft labeling